THE PREPARATION OF THE OPTICAL ISOMERS OF MIOTINE.

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THE PREPARATION OF THE OPTICAL ISOMERS OF MIOTINE.

The classical work of Pasteur on the resolution of racemic tartaric acid was quickly followed by the discovery by the same author that certain micro-organisms destroyed one or other of the enantiomorphs preferentially. Since that time numerous investigations dealing with the relationship of optically active substances to biological processes have been carried out, many of which have been concerned with the preferential action of enzymes on one isomeride of an optically active substance. Amongst the latter type of investigation may be mentioned Fischer's well known work on the relationship of configuration to fermentation amongst the hexoses and Dakin's discovery (J. Physiol., 1903-4, 30, 253; 1905, 32, 199),recently again brought into prominence, and elaborated by Willstätter and Memmen (Z. physiol. Chem. 1924, 138, 216), Willstätter, Haurowitz and Memmen (ibid. 1924, 140, 203), Willstätter and Kumagawa (ibid. 1925, 146, 151), Willstätter, Kuhn and Bamann (Ber., 1928, 61,B. 886), Willstätter, Bamann/

Bamann and Waldschmidt-Graser (Z. physiol. Chem., 1928, 173, 155), Rona and Ammon (Biochem. Z. 1927, 181, 49), Rona and Itelsohn-Schechter (ibid. 1928, 197, 482), Weber and Ammon (ibid. 1929, 204, 197) Rona and Ammon (ibid. 1930, 217, 34), Rona, Ammon and Werner (ibid. 1930, 217, 42; 221, 381) , Rona, Fischgold and Ammon (ibid. 1930, 228, 77), Bamann (Ber. 1929, 62 B., 1539) and Bamann and Laeverenz (ibid. 1930, 63 B., 394; 1931, 64 B., 897), that when the lipase from a pig's liver hydrolyses esters of racemic mandelic acid, it attacks the dextro forms preferentially. While this and similar aspects of the behaviour of optical isomerides has received such detailed consideration, investigations on the related subject of the pharmacological action of optical isomerides have been fewer in number and of more recent date. Nevertheless it is a well known and firmly established fact that the activities of optical isomerides on living organisms frequently, although not invariably, differ considerably in magnitude.

The work which has been carried out on this subject was recently ably summarised by the late Professor A.R.Cushny of Edinburgh University, a pioneer investigator in this field, in the Dohme Lectures which he delivered at Johns Hopkins University/

University, Baltimore, in 1925 and which were subsequently published in book form (Biological Relations of Optically Isomeric Substances", Williams and Wilkins, Baltimore). Cushny states (p. 38):"Many attempts have been made to compare the pharmacological and toxicological effects of pairs of optical isomers. Some of these have been done with more zeal than judgment, and unfortunately their erroneous results have been propagated by one writer after another, apparently without reading the original papers or at any rate without regarding them critically", and points out (p. 37) that "the first definite example of difference in the pharmacological action proper between the optical isomers was offered by l- and dl-hyoscyamine (atropine)" which he himself investigated (J. Physiol. 1904, 30, 176). This was followed by investigations on l- and dl- hyoscine (Cushny and Peebles, J. Physiol. 1905, 32, 501), d- and dl-homatropine (Cushny, J. Pharm. Exp. Ther., 1920, 15, 105), l- and dl-adrenaline (J. Physiol. 1908, 37, 130) and, more recently on a number of other substances. The net result of these investigations is to demonstrate that, while in the cases of many substances capable of existing in optically active forms and possessing pharmacological activities of a pronounced and specific nature, one isomeride frequently exhibits/

exhibits a physiological activity which, although qualitatively identical with that of its enantiomorph, is nevertheless of a different order of magnitude, this is by no means an invariable rule. In fact, as Cushny states (p. 60) "The most pronounced differences in the behaviour of the isomers are confined to the three series which" he "was fortunate enough to meet early in" his "work - the hyoscyamines, hyoscines and adrenaline and to the series studied by Laidlaw, in which the asymmetry of the carbon is complicated by that of the nitrogen", the latter series consisting of the canadine methochlorides (Laidlaw, J. Pharm. Exp. Ther. 1912-13, 4,461). In these cases the differences between the physiological activities of the isomerides are extremely marked. Thus, Cushny (J. Pharm. Exp. Ther., 1920, 15, 105) estimates that l-hyoscyamine is twenty times as active as its isomeride, that l-hyoscine (J. Pharm. Exp. Ther., 1921, 17, 41) is 16 to 18 times as active as the dextro form, that l-adrenaline (J. Physiol. 1909, 38, 259) is 12 to 15 times more active than its enantiomorph, while Laidlaw (loc. cit.) found differences of nearly the same order of magnitude between the physiological activities/

activities of the l- and d-forms of both the α and β canadine methochloride, the dextro form being, in each case, the more active. On the other hand the homatropines do not exhibit such marked differences, for, according to Cushny (J. Pharm. Exp. Ther., 1920, 15, 105) the activity of the laevo form is only approximately twice that of its isomeride, while no difference has been detected between the local anaesthetic activities of d- and l-β-eucaines (King, J.C.S., 1924, 125, 41), the toxic properties of d- and l-coniine (Ladenburg and Zalek, Ann. 1888, 247, 83), or the activities on the frog's heart of d- and l-tetrahydroquinaldine (Dale and Mines, J. Physiol. 1911, 42, 31-), and similar results have been obtained with a number of other substances. A more recent example in which differences have been observed between the physiological properties of optical isomerides is that of thyroxine. According to Harington (Biochem. J. 1928, 22, 1451) the laevo form is about three times as active physiologically as the dextro compound.

The relationship between the pharmacological activities of optical isomerides is, however, not so simple as might appear from the above experiments. In some respects the two isomerides may show marked differences in activity, whereas in others they may be indistinguishable. Some quotations from Cushny's/

Cushny's book will make this point clear. With respect to his comparison of l-hyoscyamine with atropine he states (p. 40): "The two bases were found to be equally poisonous to many organs such as the heart, muscle and motor nerve ends in the frog, while atropine was more excitant in the central nervous system in these animals than l-hyoscyamine and this action lasted longer. In the mammals, many organs were unaffected by even large doses, and some others, such as the heart, muscle and central nervous system reacted to the same extent to the isomers, but in a number of instances I found that l-hyoscyamine was almost exactly twice as powerful as atropine. This was seen in the more specific actions of this group on the termination of the autonomic nervous system, such as the myoneural junctions of the inhibitory fibres in the heart, of the motor oculi in the iris and of the secretory fibres in the submaxillary glands of the dog; the same ratio between the isomers holds for the intestine and other organs in which the action of atropine is not apparently exerted on the actual nerve terminations". A similar state of affairs exists in the case of the hyoscines. Thus (Cushny, p. 44) : "Another series of observations was made in/

in the same way on l- and dl-hyoscine and gave the same results on the peripheral nervous terminations, the l-base acting almost exactly twice as strongly as the dl-one on the cardiac inhibitory, the oculomotor and the secretory nerves to the salivary glands..... As regards the action on other tissues the two isomeric hyoscines appear to be equivalent except that the d- maintained its effect longer, probably from being excreted or destroyed more slowly. The effect on the human brain of l- and dl-hyoscines was compared without obvious differences being detected (Richards and Light ; see Cushny and Peebles, J. Physiol. 1905, 32, 501), but more recently Dr Moir in examining the efficacy of d- and l-hyoscine in "twilight sleep" found little or no effect from d-hyoscine, while the l-isomer was efficient, so that the l-hyoscine appears to act more strongly on the central nervous system." Why the ratio of the physiological activities of two isomerides should vary with different organs has not been explained, nor has indeed, a convincing explanation been offered of different activities of two optical isomerides. Cushny was clearly of opinion that when the pharmacological activities of/

of two optical isomerides are different this indicates that the action of the drug is caused partly, if not wholly, by its chemical union with some tissue constituent, for he states (p. 76):"I think it is beyond question that the differences in the reaction of the two components of atropine on the salivary glands on the one hand and to such substances as camphor-sulphonic acid on the other are of the same essential nature, each depending on the union of two optically active substances". If such be the case it is evident that comparisons of the pharmacological activities of optical isomerides should serve not only to assist in the elucidation of the mechanism of the action of drugs in general, but also in differentiating between those nervous responses of an organism which possess common and those which possess different mechanisms.

In view of the possible importance to physiological science of the results which might be obtained by a study of the action of optical isomerides ~~on living isomerides~~ on living organisms or surviving tissue, it is a matter for speculation why relatively few investigations of this nature have hitherto/

hitherto been recorded. The probable explanation is to be found from an examination of Cushny's work. In the three cases in which he found striking differences between the activities of the optical isomerides, namely with hyoscyamine, hyoscine and adrenaline, not only did his initial experiments consist of a comparison of the laevo with the racemic form, but the bulk of his conclusions were derived from such studies and it was only subsequently that he was able to test certain of these conclusions with the enantiomorphic compounds. Now, in each case the optically active form of the base which he employed was the one which occurs naturally, while the corresponding racemic compound could either be readily obtained from this by racemisation or was available, as in the case of adrenaline, as a synthetic product. It is clear from this that the factor which limits the extension of work of this nature is the lack of supplies of the optical isomerides of suitable substances, which may arise from an absence of co-operation between the pharmacologist and the chemist or from technical difficulties in the preparation and resolution of suitable substances.

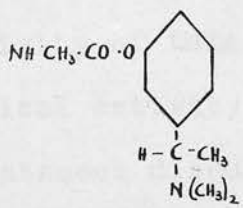
Both/

Both factors no doubt contribute towards the final result. That the difficulties experienced in the resolution of compounds of a suitable type do actually retard the prosecution of such investigations is evident from a consideration of the history of the synthetic preparation of adrenaline, which was first achieved in 1904. Its resolution however was not effected until four years later, the bitartrate being utilised for this purpose. But even then success was only achieved on account of the fact that a specimen of natural adrenaline was available, the bitartrate of which was used for inoculation purposes.

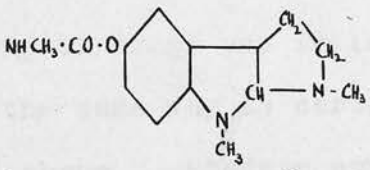
With the above considerations in mind, the present investigation was undertaken with the object of developing a method for the preparation of the stereoisomerides of the methyl urethane of α-m-hydroxyphenylethyldimethylamine (formula I) in amounts which would render them available for pharmacological and similar investigations. The substance in question was first prepared by Stedman and Stedman (J.C.S. 1929, 609) in connection with their studies on the relationship between chemical constitution and physiological action. It had

been/

been shown by Stedman (Biochem. J. 1926, 20, 719) that the power possessed by physostigmine, the constitution of which is, according to Stedman and Barger (J.C.S., 1925, 127, 247) represented by formula II, of producing a constriction of the



I.



II.

pupil when instilled into the eye, was associated with the presence of the urethane grouping in the molecule, and a number of simpler urethanes were prepared (Stedman, Biochem. J. 1929, 23, 17; Stedman and Stedman, J.C.S., 1931, 1126) which were found to exhibit similar physiological properties. A new relationship between chemical constitution and physiological action was thus established and it was concluded that substances which were basically substituted phenyl-esters of carbamic acids would, in general, possess miotic properties, although these properties could be diminished or even abolished by the introduction of certain substituents into the molecule. The preparation of the methyl urethane/

urethane of α-m-hydroxyphenylethyldimethylamine and its position isomerides was effected (Stedman and Stedman, loc. cit.) because these substances contain an asymmetric carbon atom and should therefore be capable of resolution, and it was considered of importance to determine whether the physiological activity of this group of drugs was influenced by optical activity in the same way as certain of the substances discussed above. Stedman and Stedman were, however, unable to effect the resolution of any of these compounds. Nevertheless, the miotic activity of the methyl urethane of racemic α-m-hydroxyphenylethyldimethylamine was found to be very great and of the same order of magnitude as that of physostigmine itself. The ortho- and para-isomerides were also miotically active but to a much smaller degree than the meta-compound. On account of its intense miotic activity the latter substance was named miotine(Stedman, Amer. J. Physiol. 1929, 90, 528) and it is proposed to adopt this name in the present investigation.

Since the work described above was carried out a number of developments have occurred in this field which render renewed attempts to resolve miotine desirable/

desirable. Racemic miotine, which was chosen because it was the most active of the synthetic miotics, has been submitted to a detailed pharmacological examination by White and Stedman (J. Pharm. Exp. Ther., 1931, 41, 259) and has been found to exert a selective action on the parasympathetic nervous system. It is in fact a parasympathetic stimulant and its physiological activity is identical with that of physostigmine, qualitatively, and practically so quantitatively. Other of the synthetic urethanes possess similar although smaller physiological activities, thus indicating the extensive nature of the relationship between chemical constitution and physiological action in this group, a result which has been recently confirmed by Aeschlimann and Reinert (J. Pharm. Exp. Ther., 1931, 43, 413) from a pharmacological examination of a large number of urethanes, many of which had been previously prepared by Stedman. Now, Loewi, in a series of brilliant investigations, the publication of which commenced in 1921 (Pflüger's Arch.) has shown that the inhibitory effect produced on the frog's heart by stimulation of the vagus nerve is due to the liberation/

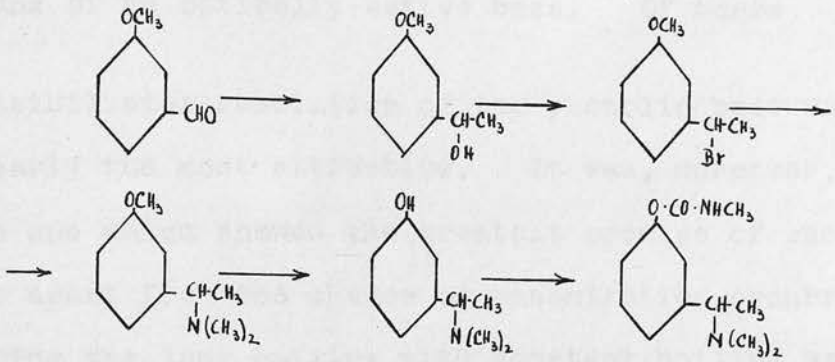
liberation of a substance in the tissue of the heart which is similar to, if not identical with, acetyl choline. Both acetyl choline and the vagus substance are destroyed by aqueous extracts of heart tissue, an effect which explains the fleeting nature of the response of this organ to stimulation of the vagus. Loewi attributed this destructive action to an enzyme present in the heart, and, since the pharmacological action of physostigmine on the heart is to sensitise it to stimulation of the vagus Loewi and Navratil (Pflüger's Arch. 1926, 214, 689) considered, and were able to show, that the effect of this alkaloid was due to its inhibiting the destruction of the vagus substance. That the destructive agent present in heart and other tissue extracts, and also in blood, possesses the properties of an enzyme has been demonstrated by Engelhart and Loewi (Arch. exp. Path. Pharm., 1930, 150, 1) and by Matthes (J. Physiol. 1930, 70, 338), but it was not certain whether it was an enzyme which acted specifically towards the vagus substance and acetyl choline or whether it was an esterase with a more general action. The experiments, moreover, were carried out with minute amounts of substrate, the destruction of which could only be followed by pharmacological/

pharmacological assays. These aspects of the problem have been examined by Stedman and Stedman (Biochem. J. 1931, 25, 1147) who have succeeded in showing that the hydrolysis of methylbutyrate and of tributyrin, processes which can be followed chemically, by a true esterase, namely liver esterase, is inhibited by minute concentrations of any of the synthetic urethanes which have been shown to possess miotic action. Considerable support was thus obtained for Loewi's view regarding the mechanism of the action of physostigmine on the heart and it may now be regarded as certain that part, if not all, of the physiological activity of both physostigmine and the synthetic urethanes is due to the inhibitory action of these substances on esterases. In view of the fact that esterases, as mentioned above, hydrolyse one component of a racemic ester, preferentially, it is to be expected that the two forms of miotine will inhibit the action of esterases to different degrees, and, if such prove to be the case, that a parallel difference will appear in their physiological activities, at any rate where this is determined by their inhibitory action towards/

towards esterases. The preparation of the optically active forms of miotine should thus be of assistance in elucidating the mechanism of the physiological action of the group of drugs under consideration, and might, moreover, render valuable information regarding the nature of enzyme action. These considerations have led to the present renewed attempt to resolve, not only miotine itself but its two position isomerides, which may be termed para- and ortho-miotine respectively.

In view of the failure of Stedman and Stedman mentioned above to effect the resolution of miotine, it was not to be expected that success in the preparation of the two enantiomorphs would be attained by crystallisation of salts of this base with optically active acids. Attempts in this direction have nevertheless been made, using a number of optically active acids. In no case, however, could a crystalline salt be obtained. It was evident that some other method would have to be adopted and consideration was first given to the possibility of resolving the compounds utilised in the synthesis of miotine. Now miotine is synthesised from m-methoxybenzaldehyde according to the following scheme:

scheme:



The aldehyde is converted by magnesium methyliodide into m-methoxyphenylmethyl-carbinol which, on treatment with dry hydrogen bromide in benzene solution, yields α-m-methoxyphenylethylbromide. The latter reacts with dimethylamine in benzene solution to form α-m-methoxyphenylethyldimethylamine, demethylation of which with constant boiling hydrobromic acid gives α-m-hydroxyphenylethyl-dimethylamine. This reacts with methyl carbimide. to form miotine. It is clear from this scheme that the desired end could be attained by resolution of either the methoxy- or the phenolic base, provided the optically active forms of these compounds could be carried through the remaining stages of the synthesis without racemisation. An alternative method would be to convert carbinol into its half ester with a dibasic acid, and to resolve this by means/

means of an optically active base. Of these possibilities resolution of the phenolic base was clearly the most attractive. It was, moreover, the one which showed the greatest promise of success, for apart from the chance of racemisation occurring during the long boiling with constant boiling hydrobromic acid necessary to demethylate the methoxy base, it has been observed that the salts of the latter exhibit(ed a much greater solubility in the ordinary solvents than did those of the phenolic base. Attempts were therefore made to prepare salts of the latter with the available optically active acids using a variety of solvents but in no case did any tendency to crystallisation become apparent. On the grounds enumerated above it appeared improbable that better results would be obtained with the methoxy base, and the use of the carbinol offered difficulties and chances of racemisation which it was desired, if possible, to avoid. The problem was therefore approached from a slightly different/

different angle. It was thought that the salts of α-m-hydroxyphenylethylmethylamine would exhibit a smaller solubility than did those of the corresponding tertiary base. If such were the case and the resolution of the secondary base thus became possible, it was obvious that a method for the preparation of the enantiomorphic miotines could be devised provided means were available for the conversion of the secondary into the tertiary base without serious loss. As will be shown below, methylation of the secondary base could be readily and smoothly effected: its resolution was therefore attempted.

The preparation of the racemic secondary base was carried out by a method similar to that employed for the tertiary base, namely by the interaction of α-m-methoxyphenylethylbromide with methylamine followed by demethylation of the methoxy group with constant boiling hydrobromic acid. It was necessary, however, to modify slightly the experimental procedure. In the preparation of the tertiary base a solution of the bromide is poured into a solution of excess

of/

of dimethylamine in benzene. This solvent could not be employed, methylamine not being sufficiently soluble in it. The reaction can however be carried out in alcoholic solution,but it takes place slowly and the yield is poor, partly, no doubt, because the alcohol itself to some extent reacts with the bromide. By using acetonitrile, in which methylamine is readily soluble, as solvent not only was the yield of secondary base considerably improved, but the action took place much more rapidly than in alcohol.

In attempting the resolution of α-m-hydroxy-phenylethylmethylamine a number of salts with optically active acids were examined. Crystalline tartrates and malates were actually obtained and some indication that a separation of the two enantiomorphs was taking place was secured, but it was evident that the difference between the solubilities of the two d-tartrates, as well as of the two l-malates, was so small that it would only be possible to obtain the two forms of the base in a pure condition after a tedious process of fractionation and in a correspondingly small yield. Since the/

the object of the present investigation was to devise a method for the preparation of d- and l-miotine in amounts suitable for use in pharmacological and biochemical work, the further examination of the tartrates and malates was abandoned and attention turned to the bromocamphor sulphonates. Owing to the deliquescent nature of bromocamphor sulphonic acid the preparation of this acid in a pure condition offers some difficulties and it is therefore usual to prepare its ammonium salt and to store the acid in this form. If the bromocamphor sulphonate of the base which it is desired to resolve will crystallise from water it is unnecessary to prepare the free acid from the ammonium salt, for the bromocamphor sulphonate of the base will crystallise from an aqueous solution of the hydrochloride of the racemic base to which an equivalent, or in some cases half an equivalent of ammonium d-bromocamphor sulphonate has been added. Ammonium d-bromocamphor sulphonate was prepared from camphor, and this method adopted, but no separation of the bromocamphor sulphonate occurred even after the mixture had been left for several days in the refrigerator. Other solvents were therefore examined. An aqueous solution of d-bromocamphor sulphonic/

sulphonic acid of known normality was prepared from the ammonium salt by the usual methods and an equivalent of the secondary base dissolved in this solution. After removal of the water by distillation under diminished pressure and drying the residue, the resulting sticky mass was taken up in ethyl acetate and left in the refrigerator. Usually no separation of crystalline meterial occurred, in which case crystallisation could be brought about by the addition of a small volume of ether, when the substance could be readily recrystallised from ethyl acetate alone. After repeated crystallisations in this way, it was evident from the rise in the melting point of the product that resolution was taking place, and it was then found that the product could be recrystallised from water to give material with a constant melting point. In view of the latter result the question of the direct preparation of the bromocamphor sulphonate from aqueous solution was re-examined, and, using the above mentioned preparation for inoculation, crystallisation readily occurred. It was subsequently found that the pure d-α-m-hydroxy-phenylethylmethylamine d-bromocamphor sulphonate separated/

separated without seeding from a solution of α-m-hydroxyphenylethylmethylamine hydrochloride in a carefully chosen volume of water on the addition of half an equivalent of d-ammonium bromocamphor sulphonate. The writer is at a loss to offer an adequate explanation of this result, which is in contradiction to the earlier experiments. It could conceivably be attributed to nuclei of the salt present in the atmosphere of the laboratory gaining access in the latter experiments to the solution and thus initiating crystallisation. It is doubtful, however, if this is the correct explanation, and the author is inclined to the view, which is suggested by the behaviour of the para isomeride described below, that in the original experiment the hydrochloride employed, although analytically pure, was contaminated with a minute amount of impurity which inhibited the crystallisation This explanation is supported by the fact that the original preparation of the base, which was employed in these experiments, was not quite colorless whereas the specimens used in the later experiments were crystallised from a different solvent/

solvent and were perfectly colorless. In any case, by ~~the~~ the following procedure described in the experimental portion, it is now possible to obtain the d-bromocamphor sulphonate of the d-base in good yield without difficulty and without seeding.

It was hoped, especially in view of the good yield of the d-base which was obtained that it would be possible to purify the l-base which remained in the mother liquors. Unfortunately this did not prove to be the case. Repeated crystallisation of the base recovered from the mother liquors had no effect on its purity. It was, it is true, possible by converting the recovered base into its hydrochloride and recrystallising this salt to obtain the pure hydrochloride of the l-base, but the yield was too small to render this a practicable method. Likewise, attempts to obtain the d-bromocamphor sulphonate of the l-base by adding d-ammonium bromocamphor sulphonate to the mother liquors proved impracticable. Ammonium l-bromocamphor sulphonate was therefore prepared from l-borneol and the pure l-α-m-hydroxyphenylethylmethylamine l-bromocamphor sulphonate obtained by the method employed in the case of the d-isomeride, using, of course, the base recovered/

recovered from the mother liquors in the preparation of the latter. The rotations of the bases recovered from the two bromocamphor sulphonates were of the same magnitude and of opposite sign, so it was therefore concluded that no racemisation had occurred during recovery despite the moderately drastic methods, described in the experimental section, which had to be employed for this purpose on account of the solubility relationships of the bases.

The procedure recently devised by Skita and Keil (Ber. 1929, 62, 1142), which consists in the catalytic reduction of a mixture of a secondary base and formaldehyde, and utilised by these authors for the conversion of dl-ephedrine into N-methyl-ephedrine, appeared to be suitable for the purpose of converting the secondary to the tertiary base and was, in fact, tested on the racemic base prior to its actual resolution. In their experiments Skita and Keil employ an aqueous solution of the hydrochloride of the base and reduce this in an atmosphere of hydrogen in the presence of formaldehyde and platinum black under an excess pressure of/

of three atmospheres. This method was tried with dl-α-m-hydroxyphenylethylmethylamine using platinum black prepared according to Willstätter and Waldschmidt-Leitz's method (Ber. 1921, 54, 113) with the modification that the pressure of hydrogen was only slightly greater than that of the atmosphere. Practically no absorption of hydrogen occurred. It was considered that this negative result might be due to the fact that the hydrochloride and not the free base was employed and a further experiment was therefore carried out in which a solution of the free base in methyl alcohol was used, the remaining procedure being identical with that previously employed. In this experiment a slow but steady absorption of hydrogen took place until the uptake almost corresponded with the amount required theoretically. On working up the product, it was not, in this case, found possible to isolate the tertiary base directly from the reaction mixture but this was readily obtained in the form of its hydrochloride. In subsequent work Adam's platinum oxide catalyst (Adam's:Organic Synthesis, vol.VIII) has been substituted for Wilstätter's platinum black and has, in fact, proved to be greatly superior.

With/

With this catalyst the hydrogenation takes place rapidly and the tertiary base can be readily obtained from the reaction product by the simple process of evaporation in vacuo of the solution obtained after removing the catalyst.

The final stage in the preparation of d- and l-miotine, effected by treating the resolved tertiary bases with methyl carbimide, proceeded smoothly and without difficulty and calls for no special comment.

The specific rotations of d- and l-miotine and of intermediates used in their preparation are tabulated below. These figures indicate that not only was resolution of the secondary base complete, but that no appreciable racemisation occurred in the subsequent stages of the synthesis.

Substance	$[\alpha]_D$ Dextro form	Laevo form.
α-m-hydroxyphenylethyl-methylamine	+ 32.0°	-32.0°
hydrochloride	+ 20.0°	-20.0°
α-m-hydroxyphenylethyl-dimethylamine	+ 55.8°	-55.8°
hydrochloride	+ 15.2°	-15.0°
Miotine	+ 37.0°	-35.7°
" hydrochloride	+ 10.6°	-10.2°

The/

The success achieved in the preparation of d- and l-miotine prompted an attempt to extend the method which had been employed to the ortho and para isomerides. On account of the fact that these isomerides are much less active physiologically than is miotine itself, their resolution was of subsidiary interest and importance. It was nevertheless felt that results of some interest might be obtained with them if the preparation of their optical isomerides could be achieved. Efforts in this direction have not, however, led to complete success. Both α-o- and α-p-hydroxyphenylethylmethylamine were prepared in pure condition. With the ortho compound no crystalline salt of the base with optically active acids could be prepared, which corresponds with the known ready solubility of the chlorides, many of which are, in fact, deliquescent, of similar ortho substituted bases in water and alcohol. In the case of the para compound, an unexpected difficulty was encountered. While well formed crystalline salts of this base with bromocamphor sulphonic and camphor sulphonic acid were obtained, these proved to be partial racemates. King (J.C.S. 1924, 125,46) found/

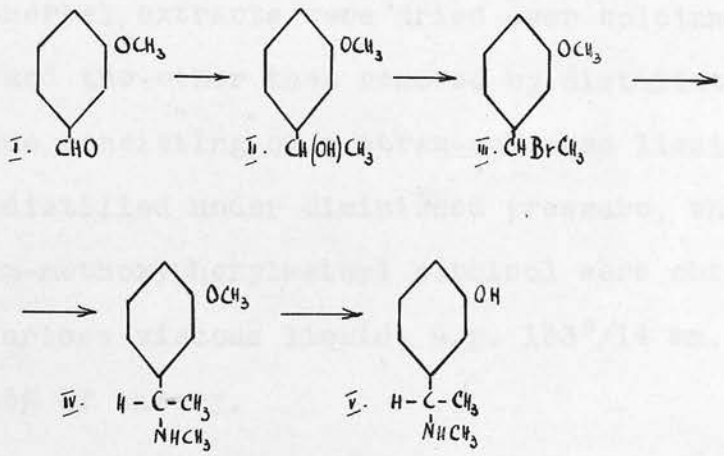
found that a similar separation of partial racemates takes place with salts of dl-β-eucaine with optically active acids. Better results were obtained with d-tartaric acid. By fractional crystallisation of the d-tartrate it was possible to isolate both d-α-p-hydroxyphenylethylmethylamine d-tartrate and the corresponding l-α-p-hydroxyphenylethylmethylamine d-tartrate in pure form. From these d- and l-bases were recovered and converted into their hydrochlorides. The rotations of the latter demonstrate that the resolution was complete. Owing to the small yield obtained, however, it was not possible to proceed with the remaining steps of the preparation.

In the crystallisation of the d-bromocamphorsulphonate of dl-α-p-hydroxyphenylethylmethylamine, it was found that prolonged heating of a solution of this salt in some way inhibited its separation, which could then only be brought about by boiling the solution with animal charcoal and filtering. The inhibition of the crystallisation was clearly caused by the presence of a decomposition product. This result appears to support the explanation offered above, of the original difficulty experienced in resolving α-m-hydroxyphenylethylmethylamine by means of its bromocamphor sulphonate.

EXPERIMENTAL.

Preparation of racemic α-m-hydroxyphenylethylmethylamine.

Racemic α-m-hydroxyphenylethylmethylamine was prepared from m-methoxybenzaldehyde according to the following scheme:-



m-Methoxyphenylmethyl carbinol.(II).

A solution of 60 gms. of m-methoxybenzaldehyde in an equal volume of dry ether was added slowly to a solution of magnesium methyl iodide prepared from 12 gms. of magnesium and 68 gms. of methyl iodide in 500 c.c. of dry ether. When the addition was complete, the solution was boiled under a reflux for about 30 minutes. On cooling, white crystals/

crystals of the addition compound separated in a solid mass round the walls of the flask. The product was decomposed by the addition of ice and sufficient hydrochloric acid to dissolve the magnesium hydroxide, care being taken to prevent the solution from becoming strongly acid. The ethereal layer was removed in a separating funnel and the aqueous solution extracted three times with ether. The united ethereal extracts were dried over calcium chloride and the ether then removed by distillation, the residue consisting of a straw-coloured liquid. This was distilled under diminished pressure, when 64 grams of m-methoxyphenylmethyl carbinol were obtained as a colourless viscous liquid, b.p. 133°/14 mm. Yield: 95% of theory.

α-m-methoxyphenylethyl bromide (III).

The carbinol from the above experiment was dissolved in 300 c.c. of benzene, solid anhydrous calcium bromide added to absorb water formed in the reaction, and the solution saturated with dry hydrogen bromide, the reaction mixture being maintained at approximately room temperature by means of a cold water bath. The brown solution so produced was/

was decanted from the calcium bromide, shaken with a further quantity of the drying agent, and the benzene and hydrogen bromide removed by distillation under diminished pressure at a bath temperature not exceeding 35°. Owing to its instability, the crude α-m-methoxyphenylethyl bromide so obtained could not be further purified by distillation but was used in this form for the preparation of α-m-methoxyphenylethylmethylamine.

α-m-methoxyphenylethyl chloride.

In view of the instability of the bromide described above, it was thought that better results might be obtained with the corresponding chloride. This was therefore prepared by adding thionyl chloride (24 c.c.) slowly to 41 gms. of m-methoxyphenylmethyl carbinol. Effervescence occurred during the addition and the reaction mixture became slightly warm. After standing for one hour the product was distilled under diminished pressure. A small quantity of thionyl chloride first passed over, the α-m-methoxyphenylethyl chloride then distilled as a colourless liquid, b.p. 110°/12 mm.

Yield: 35 gms. i.e. 75% of the theoretical.

Despite/

Despite its greater stability, this chloride did not prove so useful as the bromide in the preparation of the secondary base.

α-m-methoxyphenylethylmethylamine (IV).

When preparing α-m-methoxyphenylethyldimethylamine, the corresponding tertiary base, Stedman and Stedman (J.C.S. 1929, 609) added a solution of the bromide in benzene to an excess of dimethylamine dissolved in the same solvent. This method was not applicable to the preparation of the secondary base owing to the small solubility of methylamine in benzene. Experiments were therefore first carried out using alcohol as solvent.

In the first experiment, α-m-methoxyphenylethyl bromide prepared from 25 gms. of the carbinol was poured into 60 c.c. of a 33% solution of methylamine in alcohol, and the mixture allowed to stand. Crystals of methylamine bromide separated overnight, but on acidifying a small test portion of the solution with dilute hydrochloric acid a pronounced turbidity was produced, indicating that the bromide had by no means been converted completely into /

into basic material. Similar test portions were removed daily and examined for the presence of non-basic material. At the end of a week a distinct turbidity was still produced but it was estimated that it was not appreciably smaller in amount than on the previous day. The product was therefore worked up at this stage. The solution was decanted from the methylamine bromide, the latter washed with alcohol, and the combined alcoholic solutions acidified with hydrochloric acid and the alcohol removed by steam distillation. After the bulk of the alcohol had passed over the distillate was observed to contain a small quantity of a colourless oil. The distillation was therefore continued until this had been completely removed. The residue in the flask was then extracted with ether, first in acid solution and then after making alkaline with sodium hydroxide. The latter extract was dried over sodium sulphate, and, after evaporation of the ether, the product distilled under diminished pressure, when 17 gms. of a colourless oil, b.p. 113.5-114.5°/ 14 mm. was obtained. The yield of the base was thus 63 per cent. of the theoretical.

A similar experiment was carried out with α-m-methoxy/

methoxyphenylethyl chloride. 35 gms. of this substance were poured into 100 c.c. of a 33% solution of methylamine in alcohol and the course of the reaction followed as in the preceding experiment. In this case, however, it was found necessary to allow the mixture to stand for 14 to 15 days, and even then some non-basic material was still present in the reaction mixture. On working up the product in the manner described above, 24 gms. of α-m-methoxyphenylethylmethylamine were obtained, representing a yield of 54% of the theoretical, based on the weight of carbinol originally employed. This was clearly less satisfactory than that obtained with the bromide and it was, moreover, evident from the course of the reaction that the interaction between methylamine and the chloride proceeds considerably more slowly than does the corresponding reaction with the bromide. In both cases a reasonable yield was obtained. It was not considered advisable to attempt to accelerate the reaction by working at higher temperatures, for apart from the difficulty of working with relatively large quantities of material in closed vessels, which this /

this would necessitate, there was the probability that the tendency shown by these compounds to form styrenes would be increased at higher temperatures. It was thus clear that the preparation of the base could be effected more rapidly and in better yield with the bromide than with the chloride, and the former was therefore always used in further experiments.

While the yield of the secondary base obtained in the preceding experiments was fairly reasonable, it was felt that it could be improved if a solvent, in which the reaction could be carried out, could be found which would not only dissolve considerable quantities of methylamine but which would be incapable of reacting with the bromide. Acetonitrile was chosen for this purpose and was, in fact, found to give a somewhat better yield. But the great advantage of this solvent lay in the fact that the reaction proceeded much more rapidly, as the following typical example shows. This procedure was therefore adopted in all subsequent preparations.

Methylamine was prepared by the slow addition of strong sodium hydroxide solution to its hydrochloride in a flask, placed in an oil bath at 110°, and /

and fitted with an upright condenser through which the gas passed to a tower filled with quicklime. The dried gas was then led into a weighed amount of acetonitrile cooled in a freezing mixture when practically complete absorption took place. By again weighing the acetonitrile after the complete decomposition of the methylamine hydrochloride the weight of methylamine absorbed could be ascertained. To a solution of 35 gms. of methylamine in 130 gms. of acetonitrile, prepared in this way, and cooled in a freezing mixture, was slowly added with gentle shaking a solution of the α-m-methoxyphenylethyl-bromide prepared from 64 gms. of the carbinol in an equal volume of acetonitrile. After standing for three days at room temperature the acetonitrile was removed by distillation and reserved for subsequent experiments. Ether was added to the residue and the methylamine hydrobromide, which had separated during the evaporation of the acetonitrile, removed by filtration. The ethereal solution was then extracted with dilute hydrochloric acid and the base precipitated from the acid extract by sodium hydroxide and extracted with ether. After drying over /

over potassium carbonate the ether was removed leaving a brown liquid which, when distilled under diminished pressure yielded 52 gms. of α-m-methoxyphenylethylmethylamine as a colourless liquid, b.p. 117-118°/15 mm. Yield: 75% of the theoretical.

The hydrochloride of α-m-methoxyphenylethylmethylamine was prepared by dissolving the base in an alcoholic solution of hydrogen chloride and adding ether, when a crystalline precipitate formed. It was recrystallised by adding ether to its alcoholic solution when it separated as colourless prisms, melting point 152-153°.

Analysis.

0.2198 g. gave 0.1557 g. of AgCl

Found Cl = 17.5%

$C_{10}H_{15}ON.HCl$ requires Cl = 17.6%

α-m-hydroxyphenylethylmethylamine (V).

The above methoxy compound (52 gms.) was dissolved in 200 c.c. of constant boiling hydrobromic acid and boiled under reflux for six hours. After removal of the hydrobromic acid by distillation under diminished pressure the residual syrup, which frequently crystallised on standing, was dissolved in water and extracted with ether to remove any non-basic impurities. Preliminary

experiment s /

experiments had shown that the phenolic base was insoluble in dry ether and only sparingly soluble in moist ether, and was, moreover, soluble in dilute aqueous solutions of alkalis. Its isolation from the above solution was therefore effected by the following procedure, which utilises the fact that the base is salted out from alkaline solutions by relatively high concentrations of sodium carbonate, a process which is assisted by saturating the solution with ether. The solution was treated with a hot saturated solution of sodium carbonate, cooled and saturated with ether. The base soon commenced to separate in solid form. After standing in the refrigerator for some hours, the separation was practically complete. The solid was then filtered, dried in a desiccator, the base extracted with hot ethyl acetate and filtered from a small quantity of sodium carbonate. On cooling the filtrate, α-m-hydroxyphenylethylmethylamine separated in solid form. It can be recrystallised, from benzene or alcohol but is best purified by recrystallisation from ethyl acetate, decolourising the solution with animal charcoal if necessary, when it forms a felted mass of needles, melting point 160°. Yield: 41 gms. i.e. 87% of the theoretical.

The hydrochloride of α-m-hydroxyphenylethyl-methyl amine /

methylamine was prepared by dissolving the base in the minimum possible quantity of an alcoholic solution of hydrogen chloride and adding dry ether. It can be recrystallised from alcohol alone, when it melts at 160°.

Analysis:

0.1969 gms. gave 0.1496 gms. AgCl

Found Cl = 18.9%

$C_9H_{13}ON.HCl$ requires Cl = 18.8%

Resolution/

Resolution of α-m-hydroxyphenylethylmethylamine.

Preliminary experiments carried out with a small specimen of ammonium bromocamphor sulphonate having indicated that the resolution of this base could probably be effected by crystallisation of its bromocamphor sulphonate, quantities of the ammonium salts of both d- and l-bromocamphor sulphonic acid were prepared according to the following methods, using a sample of d-camphor as a starting point for the former, and one of l-borneol for the latter.

Preparation of l-camphor.

This was carried out according to the procedure of Wallbaum (J. für prakt. Chem. 1894, 2, 49, and Ullmann's Org. Chem. Prakt. p. 235) . 150 c.c. of concentrated nitric acid of specific gravity 1.42 and 28 c.c. of fuming nitric acid of specific gravity 1.5 were mixed in a 100 c.c. flask and cooled to 20°C. 100 gms. of l-borneol were added slowly and in small quantities with constant shaking, the temperature being kept below 20°C. After all the borneol had been added, the mixture was stirred for half an hour and was then poured on to crushed ice, when the camphor separated. This crude product which was contaminated/

contaminated with oxides of nitrogen was filtered and washed with a little ice-water. It was then transferred to a 2 litre flask, and a solution of 10 gms. of sodium hydroxide and 15 gms. of potassium permanganate in water added. The camphor was then separated by steam distillation. The white product was dried by grinding it with a small quantity of ether, spreading it in a thin layer on a large sheet of filter paper and exposing it to the atmosphere for 24 hours. Unless this procedure was adopted, it was found that the camphor would not react with the bromine.

Yield 50 gms. M.P. 172-175°C.

Preparation of α-bromocamphor.

The same process was applied to commercial d-camphor and to the l-camphor prepared according to the preceding method. The process employed is that described by Armstrong and Matthews (Chem. News, 1887, 37, 4). 150 gms. of camphor were placed in a large flask and heated on a boiling water bath. Bromine was then added slowly. Fumes of hydrogen bromide were rapidly evolved, and the contents of the flask slowly liquified. The addition of the bromine was continued until the

theoretical/

theoretical amount (51 c.c.) had been employed. On completion of the bromination, the almost colourless product was poured into a large volume of water, the solid which separated filtered, washed with water and crystallised from alcohol. Two such crystallisations generally sufficed to give pure α-bromocamphor of m.p. 76°C. Yield: 120 gms. The specific rotation of the dextro compound was measured and found to be $[\alpha]_D = +118°$ in agreement with the value given by Pope and Harvey (J.C.S. 1901, 79, 76).

Preparation of ammonium d- and l-α-bromocamphor-π-sulphonates.

The sulphonation of the bromocamphors was first attempted by the method of Kipping and Pope (J.C.S. 1895, 67, 356) using chlorosulphonic acid as sulphonating agent, but it was found to be more convenient, as pointed out by Pope and Read (J.C.S. 1910, 97, 2200) to use the earlier method of these authors (J.C.S. 1893, 63, 577). A mixture of fuming and concentrated sulphuric acid was made up to a specific gravity of 1.865 at 15°C. and consisted of 270 c.c. of concentrated sulphuric acid with 170 c.c. of/

of the fuming acid. On addition of 95 gms. of α-bromocamphor to 275 c.c. of this acid at room temperature, solution readily took place and the temperature of the reaction mixture rose simultaneously to about 50°. After being stirred for about 30 seconds, the mixture was poured through a large funnel filled with crushed ice, when an almost insignificant amount of bromocamphor separated. The solution was almost neutralised with calcium hydroxide and the process completed with calcium carbonate. The calcium sulphate was removed by filtration, well washed with water, and the combined filtrates and washings were treated with ammonium carbonate and again filtered. The filtrate was concentrated until the ammonium d-bromocamphor-π-sulphonate separated. After cooling, this was filtered, washed with rectified spirit and recrystallised from water.

The above process worked smoothly with both d- and l-bromocamphor provided the specific gravity of the acid used was carefully adjusted. If the acid was too concentrated, carbonisation occurred in the reaction mixture, torrents of sulphur dioxide being simultaneously evolved.

Preparation/

Preparation of a solution of d-α-bromocamphor-π-sulphonic acid.

Following the procedure described by Pope and Peachey (J.C.S. 1898, 73, 895), 100 gms. of the ammonium salt were treated with an aqueous solution containing an excess of barium hydroxide and the mixture boiled in an evaporating basin until the ammonia had been completely expelled. The excess baryta was removed by passing carbon dioxide through the boiling solution and filtering. The barium bromocamphor sulphonate was now decomposed by the addition of the exact amount of sulphuric acid necessary to precipitate the barium quantitatively. After filtration, the solution was made up to 500 c.c. and titrated, when it was found to be 0.584 N, corresponding with a yield of 90.8 gms. of acid from 100 gms. of ammonium salt.

Resolution of α-m-hydroxyphenylethylmethylamine.

30 Grams of the racemic base were dissolved in 345 c.c. of a 0.584 N solution of d-bromocamphor sulphonic acid and the water removed as completely as possible by distillation in vacuo. In order to remove last traces of water, the sticky brown residue was dissolved in alcohol and the solvent similarly/

similarly removed, this process being again repeated. The residue was now dissolved in about 220 c.c. of hot ethyl acetate and the solution cooled and placed in the refrigerator. After two days the crystalline material which had separated was filtered. This fraction weighed 46 gms. and melted at 165°C. Addition of ether to the mother liquors caused a further 20 gms. of material to separate. This, however, melted at about 166° and was evidently not essentially different from the first fraction. Small preliminary experiments had shown that further crystallisation from ethyl acetate produced a rise in the melting point of the product, which could then be crystallised from water. In the present experiment this further crystallisation from ethyl acetate was avoided and the two fractions were dissolved separately in hot water, the first fraction of 46 gms. in 150 c.c. and the second of 20 gms. in 45 c.c. The two solutions were rapidly cooled and inoculated with some crystals of d-bromocamphor sulphonate of the base which had been obtained in the preliminary experiments referred to above. In both cases crystalline material separated rapidly at room temperature.

The/

The crystals were filtered after about two hours, and both batches melted at about 191°. Yield: 15.5 and 6.8 gms. respectively. Further crystallisation produced no change in the melting point. It was subsequently found that this salt contains an indefinite amount of water of crystallisation which it loses slowly when exposed to the atmosphere and more rapidly in a desiccator. The anhydrous substance which can also be obtained by recrystallisation of a hydrated specimen from ethyl acetate, melted at 197°. As will be shown below this was the pure d-α-m-hydroxyphenylethylmethylamine d-bromocamphor sulphonate. The base was recovered by the procedure employed with the racemic compound and recrystallised from ethyl acetate, when it melted at 172°. The hydrochloride melted at 200°. The latter proved to be dextro rotatory, a solution prepared by dissolving 0.1 gms. in 2 c.c. of water giving when examined in a polarimeter a rotation of $\alpha_D = + 0.93°$, a decimeter tube being used.

Attempts to obtain pure l-α-m-hydroxyphenylethylmethylamine from the various mother liquors from the preparation of the d-α-m-hydroxyphenylethylmethylamine d-bromocamphor sulphonate were not completely successful. The base recovered

from/

from these mother liquors melted at about 164° and this melting point was not raised on further crystallisation from ethyl acetate. On converting this base into its hydrochloride and recrystallising it from alcohol and ether, a hydrochloride melting at 200° was obtained which was clearly a salt of the pure laevo base. With a solution prepared by dissolving 0.2 gms. of the salt in 2 c.c. of water a rotation of $[\alpha]_D$ = - 1.98 was observed.

The above experiments served to establish the melting points of d-α-m-hydroxyphenylethylmethylamine d-bromocamphor sulphonate as well as those of the resolved base and hydrochlorides, and to give information regarding the solubilities of the various products. The yields were not, however, as satisfactory as was desired. On account of the relatively small solubility of the bromocamphor sulphonate in water, it was decided, especially in view of the fact that crystals of the required salt were now available to serve as nuclei, to attempt to effect the resolution of the base by dissolving a mixture of ammonium d-bromocamphor sulphonate and the hydrochloride of the racemic base in water, a method which had yielded no result in preliminary experiments. This method now proved to be successful, at first with, and/

and finally, without inoculation with the crystals obtained as described above. The final details adopted are given in the next paragraph.

60 Grams of the hydrochloride of α-m-hydroxyphenylethylmethylamine were mixed with 55 gms. (slightly) more than half a molecular proportion) of ammonium d-bromocamphor sulphonate and the mixture dissolved in 295 c.c. of hot water. The solution was cooled rapidly and the salt soon commenced to separate. After standing for about three hours at room temperature and with occasional shaking, the product was filtered when 62 gms. of crystalline material. m.p. 187-190° were obtained. On standing in the refrigerator overnight, the mother liquors deposited a further crop of crystals (5 gms.), melting at 182-185°, which on recrystallisation from water gave 4 gms. of material melting at 188-190° . These were united with the first batch and the 66 gms. of salt thus obtained were recrystallised from water and yielded 59 gms. of bromocamphor sulphonate, melting at 193° after drying for a short time in a vacuum desiccator. Yield: 79% of the theoretical.

d-α-m-hydroxyphenylethylmethylamine d-α-bromocamphor-π'-sulphonate crystallises from water in the form of rectangular tablets which contain an indefinite/

indefinite amount of water of crystallisation. This is lost slowly in the air and more rapidly in a vacuum desiccator over sulphuric acid. The anhydrous salt which melts at 197° can be obtained directly by crystallisation of the hydrated substance from ethyl acetate, in which it is sparingly soluble at room temperature. The salt is also sparingly soluble in methyl and ethyl alcohols.

Analysis/

Analysis:

5.122 mg. of air dried substance when dried in a high vacuum over P_2O_5 lost 0.243 mg.

4.875 mg. of anhydrous substance gave 8.865 mg. CO_2 and 2.650 mg. H_2O.

Found: C = 49.6%, H = 6.0%.

$C_9H_{13}ON.C_{10}H_{14}OBrSO_3H$ requires C = 49.3%, H = 6.1%.

Preliminary experiments having shown that the separation of the d-bromocamphor sulphonate of the d-base described above was due less to any great difference in the solubilities of the two d-bromo-camphor sulphonates than to the greater tendency to supersaturation shown by the d-bromo-camphor sulphonate of the l-base, it was thought that it might be possible to prepare and purify the latter salt by the addition of a further half molecular proportion of ammonium d-bromocamphor sulphonate to the mother liquors from the experiment described in the preceding paragraph. While this caused the precipitation of the bulk of the remaining material, it was found impracticable to purify this by crystallisation. The base was therefore recovered and recrystallised. In confirmation of the

experiments/

experiments previously described this was not found to effect any further purification. It was therefore converted into the hydrochloride, which, on recrystallisation, yielded a small quantity of the pure salt of the l-base, but the yield was too small for this method to be of service in the preparation of l-miotine. 23 Grams of impure l-hydrochloride were therefore mixed with 40 gms. of ammonium l-bromocamphor sulphonate and dissolved in 120 c.c. of hot water. After cooling and allowing to stand for three hours, with occasional shaking, the crystalline salt which had separated was filtered. Yield: 47 gms. M.P. 192°. This was recrystallised from water and dried for a few hours in a vacuum desiccator when it melted at 193°. The properties of the l-α-m-hydroxyphenylethylmethylamine-l-bromo-camphor sulphonate are, of course, identical with those of the corresponding d-α-salt.

Analysis:

10.605 mgm. of air dried substance when dried in a high vacuum over P_2O_5 lost 0.354 mg.

10.251 mg. of anhydrous substance gave 5.145 mg. of $BaSO_4$.

Found: S = 6.9%

$C_9H_{13}ON_1C_{10}H_{14}OBrSO_3H$ requires S = 6.9%

Owing to the sparing solubilities of the above bromo-camphor/

camphor sulphonates in all ordinary solvents at room temperature, their rotations were not determined. The resolution was controlled by following the melting point of the various fractions during fractional crystallisation and by the rotation of the recovered bases.

d-α-m-hydroxyphenylethylmethylamine was recovered from its bromocamphor sulphonate by the method described in connection with the racemic base, and recrystallised from ethyl acetate. 50 Grams of the bromocamphor sulphonate gave 14 gms. of the pure base, i.e. 87% of the theory. d-α-m-hydroxyphenylethylmethylamine crystallises from ethyl acetate in a felted mass of needles, m.p. 171°.

Analysis:

5.181 mg. gave 13.600 mg. CO_2 and 3.950 mg. H_2O

Found: C = 71.6%, H = 8.5%

$C_9H_{13}ON$ requires C = 71.5%, H = 8.6%

Rotation.

0.1000 Grams was dissolved in 2 c.c. of pyridine. The value obtained for this solution in a decimetre tube was $[\alpha]_D$ = + 3.2. On the assumption/

assumption that no change was produced in the volume of the solvent, which is only approximately correct, this gives $[\alpha]_D$ = + 64.0°.

Owing to the small solubility of this base in other solvents, its rotation had to be determined in pyridine solution. It was found, however, that with different specimens of 'pure' pyridine widely different values were obtained, no doubt on account of the varying amounts of water which were present in these samples. In view of the known difficulty of preparing absolutely anhydrous pyridine the specific rotation in this solvent was not determined accurately. It was thought sufficient to compare the rotations of the d- and l-forms, under identical conditions. As can be seen from the experimental results identical values were thus obtained, indicating the completeness of the resolution.

The hydrochloride of d-α-m-hydroxyphenylethylmethylamine was prepared by dissolving the d- base in a solution of hydrogen chloride in alcohol and adding ether. The precipitated salt was filtered and recrystallised from alcohol when it formed hexagonal tablets, m.p. 201°.

Analysis/

Analysis:

2.913 mg. gave 0.548 mg. Cl.

Found Cl = 18.8%.

$C_9H_{13}ON_1HCl$ requires Cl = 18.9%

Rotation.

0.2000 Grams was dissolved in water and diluted to 2 c.c. The value obtained for this solution in a decimetre tube was $\alpha_D = +2.00°$. Hence $[\alpha]_D = 20.0°$

l-α-m-hydroxyphenylethylmethylamine, when recovered from its bromocamphor sulphonate, melted at 171°. Its properties were identical with those of the dextro isomeride, described above.

Analysis:

2.983 mg. gave 0.245 c.c. of N at 23°C. and 749mm.

Found N = 9.1%

$C_9H_{13}ON$ requires N = 9.3%

Rotation.

0.1000 Grams was dissolved in 2 c.c. of pyridine. The values obtained in a decimetre tube was $\alpha_D = 3{\cdot}2°$. This gave, as with the dextro isomeride $[\alpha]_D = -64.0°$.

The/

The hydrochloride of l-α-m-hydroxyphenylethyl-methylamine melted, in agreement with the d-isomeride, at 201° and in all other respects agreed with the latter in properties.

Analysis:

3.543 mg. gave 0.683 mg. Cl

Found Cl = 19.3%.

$C_9H_{13}ON$ HCl requires Cl = 18.9%.

Rotation.

0.2000 Grams was dissolved in water and diluted to 2 c.c. The value obtained for this solution in a decimetre tube was $\alpha_D = -2.00°$. Hence $[\alpha]_D = -20.0°$.

Preparation of d- and l-hydroxyphenylethyldimethylamine.

The preparation of d- and l-miotine from the above secondary base in reasonable yield was only rendered possible on account of the development of a method for the conversion of secondary into tertiary bases in practically quantitative yield. This method was devised by Skita and Keil (Ber. 1929, 62, 1142) and consists in reducing a mixture of the secondary base and formaldehyde, catalytically, using platinum black as catalyst. Before proceeding with/

with the resolution described above the method was tested on dl-α-m-hydroxyphenylethylmethylamine. In employing this method for the preparation of methylephedrine, Skita and Keil dissolved their base in dilute hydrochloric acid and after the addition of the requisite amount of formaldehyde, reduced the mixture with hydrogen in the presence of platinum black and under a total pressure of four atmospheres. In the absence of apparatus suitable for use with such high pressures, an attempt was made to carry out the methylation at a pressure which was virtually that of one atmosphere. An apparatus similar to that described by Hess (Ber. 1913, 46, 3120) and colloidal platinum prepared according to Willstätter and Waldschmidt-Leitz (Ber., 1921, 54, 113) was used for this purpose. A slow absorption of hydrogen occurred, but this ceased before a quarter of the theoretical amount had been taken up. This failure was attributed to the fact that the amine was present in the form of its hydrochloride rather than as free base, for it is notorious that, using the customary methylating agents, methylations of amines proceed with much greater difficulty with the salt than with the free base. A second experiment was therefore carried out under the same conditions except that a solution

of/

of the free base in methyl alcohol was used. With this experiment there was a steady absorption of hydrogen, which ceased when slightly less than the theoretical amount had been absorbed. The catalyst was removed by filtration, the solvent evaporated and the residual syrup placed in a vacuum desiccator to remove last traces of solvent and of formaldehyde. The product failed, however, to crystallise. It was therefore converted into the hydrochloride by dissolving it in a solution of hydrogen chloride in alcohol. Addition to this of dry ether precipitated an oil, which, after decanting the solvents, was washed with dry ether. On dissolving this oil in hot acetone, a crystalline hydrochloride separated on cooling which melted at 198° and proved to be identical with a specimen of the hydrochloride of α-m-hydroxyphenylethyl-dimethylamine prepared by Stedman and Stedman (J.C.S. 1929, 613). It was thus evident that with the modified procedure methylation could be effected. No further experiments were made with the dl-base. When the method was applied to the resolved bases, the catalyst was prepared in the form of platinum oxide according to Adam's method (Adam's: Organic Syntheses/

Syntheses, vol. VIII). This proved to be much more efficient than Willstätter and Waldschmidt-Leitz's catalyst, for the absorption of hydrogen took place much more rapidly, and the tertiary base could be readily obtained from the product, as will be seen from the following typical example.

5 Grams of d-α-m-hydroxyphenylethylmethylamine were dissolved in 30 c.c. of hot methyl alcohol and 3 c.c. of formalin were added. The mixture was then cooled and introduced into the hydrogenation chamber of the apparatus, which was then evacuated and swept out with hydrogen, the latter being generated from pure zinc in a Kipp's apparatus and washed successively with solutions of potassium permanganate and silver nitrate. The hydrogenation vessel was then practically evacuated, the hydrogenation chamber shut off from the remainder of the apparatus and 0.1 gms. of platinum oxide washed into the upper and smaller chamber with methyl alcohol. Connection was now made with the burette containing hydrogen and the apparatus shaken until the platinum oxide was completely reduced, when it was transferred to the adjoining chamber containing the reaction mixture. After

taking/

taking the burette reading the apparatus was again shaken, when a rapid and steady absorption of hydrogen occurred. In the first 40 minutes 700 c.c. were taken up, and in the succeeding 15 minutes a further 50 c.c. were absorbed. The total volume of hydrogen absorbed was somewhat less than that required theoretically (81 c.c.), but the absorption was now very slow and experience had shown that the best product was obtained if the process was stopped at this stage. The catalyst was therefore filtered and the methyl alcohol evaporated, the syrupy residue being dried in a vacuum desiccator. After about 12 hours, it had completely solidified. Yield 5.2 gms. This impure product was crystallised from a small volume of alcohol when 3.8 gms. of material were obtained, while a further 0.5 gms. was recovered from the alcoholic mother liquors in the form of hydrochloride. d-α-m-hydroxyphenylethyldimethylamine crystallises from benzene in square tablets which melt at 116°.

Analysis:

4.996 mg. gave 13.300 mg. CO_2 and 4.130 mg. H_2O

Found C = 72.6%, H = 9.2%

$C_{10}H_{15}ON$ requires C = 72.7%, H = 9.1%

Rotation/

Rotation.

0.1000 gm. was dissolved in alcohol and diluted to 2 c.c. The value obtained for this solution in a decimeter tube was α_D = + 2.79°. Hence $[\alpha]_D$ = + 55.8°.

The hydrochloride of d-α-m-hydroxyphenylethyldimethylamine crystallises from alcohol on the addition of ether in aggregates of tablets which melt at 161°.

Analysis:

3.191 mg. gave 0.573 mg. Cl

Found Cl = 17.9%

$C_{10}H_{16}ON.HCl$ requires Cl = 17.6%

Rotation.

0.2000 gm. was dissolved in water and diluted to 2 c.c. The value obtained for this solution in a decimeter tube was α_D = + 1.52°. Hence $[\alpha]_D$ = + 15.2°.

l-α-m-hydroxyphenylethyldimethylamine was prepared from the corresponding secondary base under the same conditions as were used for its optical isomeride. It melted at 116°.

Analysis:

3.339 mg. gave 0.249 c.c. of N at 25° and 749 mm.

Found N = 8.2%

$C_{10}H_{15}ON$ requires N = 8.5%

Rotation.

0.1000 gm. was dissolved in alcohol and diluted to 2 c.c. The value obtained for this solution in a decimeter tube was $\alpha_D = -2.79°$. Hence $[\alpha]_D = -55.8°$.

The hydrochloride of l-α-m-hydroxyphenylethyl-dimethylamine melts at 161°.

Analysis:

3.068 mg. gave 0.543 mg. Cl

Found Cl = 17.7%

$C_{10}H_{15}ON.HCl$ requires Cl = 17.6%

Rotation.

0.2000 gms. was dissolved in water and diluted to 2 c.c. The value obtained for this solution in a decimeter tube was $\alpha_D = -1.50°$. Hence $[\alpha]_D = -15.0°$.

Preparation of the methylurethanes of d- and l-α-m-hydroxyphenylethyldimethylamine (d- and l-miotine).

The method adopted for the conversion of d- and l-α-m-hydroxyphenylethyldimethylamine into the corresponding miotines was that utilised by Stedman and Stedman (J.C.S. 1929, 609) when preparing dl-miotine.

4 gms. of the d-(or l-) tertiary base was treated with about 4 c.c. of freshly prepared methyl carbimide, the mixture being kept cool. The base dissolved and after about 10 minutes, a crystalline product commenced to separate from the solution. The reaction mixture was allowed to stand overnight at room temperature, when the excess of methyl carbimide was removed in a vacuum desiccator. The residue was dissolved in warm ether and the solution of the base thus obtained filtered from a small quantity of brown material. On evaporation of the ether a colourless solid product was obtained. Yield: 4.5 gms. This was crystallised from ether, in which it was moderately soluble, when d-(and l-) α-m-hydroxyphenylethyldimethylamine (d-(and l-)miotine) were obtained in the form of flat prisms, m.p. 85°.

Analysis:

d-miotine.

4.838 mg. gave 11.475 mg. CO_2 and 3.550 mg. H_2O

Found C = 64.7%, H = 8.2%.

$C_{12}H_{18}N_2O_2$ requires C = 64.9%, H = 8.1%

l-miotine.

2.839 mg. gave 0.315 c.c. of N_2 at 23° and 747 mm.

Found N = 12.3%

$C_{12}H_{18}N_2O_2$ requires N = 12.6%

Rotation/

Rotation.

d-miotine.

0.2000 gms. was dissolved in alcohol and diluted to 2 c.c. The value obtained for this solution in a decimeter tube was $\alpha_D = + 3.70°$. Hence $[\alpha]_D = +37.0°$.

l-miotine.

0.2000 gms. was dissolved in alcohol and diluted to 2 c.c. The value obtained for this solution in a decimeter tube was $\alpha_D = -3.57°$. Hence $[\alpha]_D = -35.7°$.

The hydrochlorides of d- and l-α-m—hydroxy-phenylethyldimethylamine (d- and l-miotine) were prepared by dissolving the corresponding bases in alcohol and adding an alcoholic solution of hydrogen chloride. The hydrochloride began to separate in a short time. Dry ether was added to complete the separation when the solution was filtered. Yield: quantitative. d-(and l-) miotine hydrochloride separates slowly from a solution in alcohol in the form of tablets, which with slow heating melt with effervescence at 167° after sintering at about 160°. As, however, this is a decomposition/

decomposition point it varies considerably with the rate of heating.

Analyses:

d-miotine hydrochloride.

3.216 mg. gave 0.433 mg. Cl.

Found Cl = 13.5%

$C_{12}H_{18}N_2O_2$ requires Cl = 13.7%

l-miotine hydrochloride.

3.110 mg. gave 0.425 mg. Cl

Found Cl = 13.7%

$C_{12}H_{18}N_2O_2$ requires Cl = 13.7%

Rotation.

d-miotine hydrochloride.

0.2000 gms. was dissolved in water and diluted to 2 c.c. The value obtained from the solution in a decimeter tube was $\alpha_D = +1.06°$. Hence $[\alpha]_D = +10.6°$.

l-miotine hydrochloride.

A similar rotation of this isomeride gave $\alpha_D = -1.02°$. Hence $[\alpha]_D = -10.2°$.

Preparation/

Preparation of α-o-hydroxyphenylethylmethylamine.

This was effected by a series of reactions similar to that used in the preparation of its m-isomeride.

By the interaction of o-methoxybenzaldehyde with magnesium methyl iodide under conditions identical, except in one detail mentioned below, with those employed in the case of the m-isomeride, crude o-methoxyphenylmethylcarbinol was obtained as a thick oil. On account of the tendency shown by this compound to lose water with the formation of a styrene, a tendency which is very pronounced in the presence of traces of hydriodic acid, it was not purified by distillation or otherwise but was used in the crude form for the next reaction. For the same reason no acid was employed during the decomposition of the addition compound, ammonium chloride was used instead to dissolve the magnesium hydroxide.

The crude carbinol was converted through the bromide into α-o-methoxyphenylethylmethylamine by the procedure described in connection with the m-isomeride. It formed a liquid with a faint greenish yellow colour which boiled at 99-101°/14 mm.

Starting/

Starting with 60 gms. of o-methoxybenzaldehyde, 45 gms. of α-o-methoxyphenylethylmethylamine, representing a yield which was 63% of that theoretically possible, was obtained.

Demethylation of the methoxy base was effected by boiling with constant boiling hydrobromic acid as described above. A slight modification in the isolation process was, however, necessary on account of the fact that removal of the methyl group proceeds much more slowly with the ortho than with the meta isomeride, and that prolonged boiling with hydrobromic acid causes considerable decomposition, in which the basic group is removed from the molecule. After boiling a solution of the methoxy base in constant boiling hydrobromic acid for about 5 hours, the hydrobromic acid was removed by distillation under diminished pressure, the residue dissolved in water, made strongly alkaline with sodium hydroxide and the solution extracted once with ether. The alkali was then neutralised and the solution again made alkaline with sodium carbonate and extracted with ether. The first ethereal extract contained a mixture of phenol and methoxy compound. The

second/

second contained only phenol, which after removal of the ether was distilled under diminished pressure. α-o-hydroxyphenylethylmethylamine boils at 108°/12 mm. The distillate rapidly solidifies on cooling. It is readily soluble in alcohol, ethyl acetate, benzene and ether but crystallises from light petroleum ~~ether~~, when it melts at 61°.

Analysis:

4.550 mg. gave 11.900 mg. CO_2 and 3.550 mg. H_2O.

Found C = 71.3%, H=8.7%

$C_9H_{13}ON$ requires C = 71.5%, H = 8.6%

It has not been found possible to prepare any crystalline salts of this phenolic base with optically active acids. The solubilities appear to be too great in all the ordinary organic solvents and in water.

Preparation of α-p-hydroxyphenylethylmethylamine.

The outline of the method employed is identical with that of the meta and ortho isomeride.

Anisaldehyde was converted into p-methoxyphenylmethylcarbinol by means of the Grignard reagent using the precautions described in connection with the ortho isomeride. By treating this successively with hydrogen bromide in benzene solution and methylamine in acetonitrile, α-p-methoxyphenylethylmethylamine was obtained as a colourless liquid, b.p. 108°/11 mm. Yield: 45 gms. from 60 gms. of anisaldehyde, i.e. 63% of the theory.

The hydrochloride of α-p-methoxyphenylethylmethylamine separated as an oil when ether was added to a solution of the base in alcoholic hydrogen chloride and then slowly solidified. When recrystallised by the addition of dry ether to its alcoholic solution it formed rosettes of prisms, m.p. 134-135°.

Analysis:

0.1821 gms. gave 0.1302 gms. of AgCl

Found Cl = 17.7%

$C_{10}H_{16}ONCl$ requires Cl = 17.6%

Demethylation of the methoxy compound was then carried/

carried out by boiling it with constant boiling hydrobromic acid. In this case, however, it was found convenient to purify the phenolic base through its hydrobromide, which was obtained as a thick brown oil, which partly crystallised on cooling, on removal of the hydrobromic acid by distillation under diminished pressure and drying the residue by repeated addition and evaporation of alcohol. The semi-crystalline hydrobromide was dissolved in alcohol and the dark solution so obtained decolorised by boiling it with animal charcoal and filtering. Addition of ether to the cooled filtrate caused the hydrobromide to separate. This was filtered and washed with acetone, which removed a little red colouring matter which tended to develop when the salt was in contact with ether and air. The slightly coloured hydrobromide was recrystallised from alcohol, when it was obtained as a colourless crystalline solid, m.p. 171°. Yield: 33 gms. from 45 gms. of the methoxy compound, i.e. 50% of the theoretical.

α-p-hydroxyphenylethylmethylamine, which resembles the meta but differs from the ortho isomeride in being insoluble in ether, was recovered from the hydrobromide by the method utilised with the meta compound/

compound. When crystallised from ethyl acetate it melted at 122-123°.

Analysis:

5.035 mg. gave 13.190 mg. CO_2 and 3.910 mg. H_2O

Found C = 71.4%, H = 8.6%

$C_9H_{13}ON$ requires C = 71.5%, H = 8.6%

The hydrochloride of α-p-hydroxyphenylethylmethylamine crystallises from alcohol and melts at 180°.

Analysis:

3.201 mg. gave 0.603 mg. of AgCl.

Found Cl = 18.8%

$C_9H_{13}ON.HCl$ requires Cl = 18.9%

Resolution of α-p-hydroxyphenylethylmethylamine.

dl-α-p-hydroxyphenylethylmethylamine d-α-bromocamphor-π-sulphonate.

Some preliminary experiments had shown that dl-α-p-hydroxyphenylethylmethylamine formed a crystalline bromocamphor sulphonate. On recovery from this salt the base was found, however, to be inactive. This was at first attributed to the action of the strong sodium carbonate solution used to decompose the/

the bromocamphor sulphonate and to salt out the base, which it was thought caused racemisation. In order to settle this point the experiment was repeated on a larger scale.

33 Grams of the hydrobromide of dl-α-p-hydroxyphenylethylmethylamine were mixed with 24.8 gms. (half molecular proportion) of ammonium d-bromocamphor sulphonate, and the mixture dissolved in 330 c.c. of hot water. On cooling 33 gms. of crystalline material, m.p. 209°, separated. This was filtered, the filtrate concentrated and a further 24.8 gms. of ammonium d-bromocamphor sulphonate was dissolved in the filtrate when a second crop of crystals was obtained. Both batches were recrystallised from water and both yielded well formed prisms which melted at 216-217°, and were apparently identical. In the recrystallisation of the first batch, however, no separation of solid at first took place nor could this be induced either by scratching the walls of the containing vessel with a glass rod or by cooling the solution, which was quite colourless, in the refrigerator. Nevertheless, it was found that by the simple expedient of/

of rapidly boiling the solution with a small amount of animal charcoal and filtering, crystallisation took place before the solution was cold. Presumably some impurity which inhibits the crystallisation was removed by the charcoal.

Both crops of crystals were examined in the polarimeter. Owing to their small solubilities in the common solvents, solutions of pyridine were used. In each case, 1 gm. of the salt was dissolved in 10 c.c. of pyridine. Using a tube of one decimeter length an α_D of +0.66 was observed with both samples. I t was evident from this as well as from the fact that the base recovered from this salt had no rotation that no resolution had been effected and that the salt was, in fact, a partial racemate.

dl-α-p-hydroxyphenylethylmethylamine-d-bromocamphor sulphonate crystallises from water in prisms, m.p. 216-217°.

Analysis:

4.705 mg. gave 8.540 mg. CO_2 and 2.550 mg. H_2O

Found C = 49.5%, H = 6.0%

$C_9H_{13}ON.C_{10}H_{14}OBrSO_3H$ requires C = 49.3%, H = 6.1%

dl-/

dl-α-p-hydroxyphenylethylmethylamine-d-camphor-10-sulphonate.

A partial racemate was also obtained with d-camphor sulphonic acid. 10 Grams of α-p-hydroxy-phenylethylmethylamine were mixed with 15.6 gms. (one equivalent) of d-camphor-10-sulphonic acid and the mixture dissolved in hot alcohol. On cooling crystals separated from the solution. These were filtered (Yield: 10 gms.) and ether added to the filtrate when a further separation of 12 gms. of solid material occurred. Both fractions melted at 175-178°. They were separately crystallised from alcohol, when the melting point of both specimens was 181°, and the same value was obtained for a mixture of the two. The rotations also proved to be identical. In each case 1 gm. of the camphor sulphonate was dissolved in 10 c.c. of water and the solution examined in a decimeter tube. Identical values of $\alpha_D = +1.33°$ were obtained, which, on the slightly incorrect assumption that the volume of the solution was 10 c.c., gave $[\alpha]_D = +13.3°$, and $M[\alpha]_D = 50.9°$. According to the literature ammonium d-camphor-10- sulphonate has a $M[\alpha]_D = 50.8°$. It is thus obvious/

obvious that no resolution had taken place, dl-α-p-hydroxyphenylethylmethylamine d-camphor-10-sulphonate crystallises from alcohol in prisms and melts at 181°.

Analysis:

4.510 mg. gave 9.845 mg. CO_2 and 2.990 H_2O

Found C = 59.5%, H = 7.4%

$C_9H_{13}ON.C_{10}H_{15}OSO_3H$ requires C = 59.5%, H = 7.6%

Dextro and laevo-α-p-hydroxyphenylethylmethylamine.

Experiments with the tartrate proved more successful. Preliminary experiments had given indications that a resolution was taking place when the tartrate was crystallised from alcohol. The following larger experiment was therefore carried out.

A mixture of 18 gms. of α-p-hydroxyphenylethylmethylamine and 18 gms. (one molecular proportion) of tartaric acid was dissolved in a small quantity of hot alcohol. On cooling and scratching the walls of the vessel with a glass rod, a separation of crystalline material immediately took place. This was filtered and dried. Yield: 30 gms. This was dissolved in 600 c.c. of/

of hot alcohol, cooled and left in the refrigerator, Crystallisation commenced after one hour and continued slowly. After 24 hours the solution was filtered giving 18 gms. of solid, m.p. 140-141°. This was now recrystallised from 50 c.c. of methyl alcohol, from which crystallisation occurred rapidly. Filtration of the solid after three hours yielded 10 gms. of material, m.p. 156-157°. Repeated recrystallisation from methyl alcohol gave 8 gms. which melted at 162° and this melting point was not changed on further recrystallisation. This substance which crystallises from alcohol in the form of rosettes proved to be d-α-p-hydroxyphenyl-ethylmethylamine-d-acid tartrate.

Analysis:

4.860 mg. gave 9.190 mg. CO_2 and 2.840 mg. H_2O

Found C = 51.6%, H = 6.5%.

$C_9H_{13}ON.(CHOHCOOH)_2$ requires C = 51.8%, H = 6.3%

Rotation.

0.2000 gms. was dissolved in 2 c.c. of water. This solution when examined in a decimeter tube gave α_D = +2.45°.

The 600 c.c. of filtrate from the above crystallisation/

crystallisation yi elding 18 gms. of solid was concentrated to 100 c.c. and treated with dry ether. This caused the immediate separation of solid which was filtered. Yield: 10 gms., m.p. 133°. Recrystallisation from 50 c.c. of ethyl alcohol, from which it separated in the form of rosettes, gave 7 gms. of material with unchanged melting point. This proved to be l-α-p-hydroxyphenyl-ethylmethylamine-d-acid tartrate.

Analysis:

2.800 mg. gave 0.117 c.c. N at 22.5° and 750 mm.

Found N = 4.7%

$C_9H_{13}ON(CHOH.COOH)_2$ requires N = 4.7%

Rotation.

0.2000 gm. was dissolved in 2 c.c. of water and the solution examined in a decimeter tube, giving α_D = +0.42.

The free base was recovered from the above tartrates by the method described in connection with the dl-base. In this way there was obtained d-α-p-hydroxyphenylethylmethylamine which crystallises from ethyl acetate and has m.p. 122°, and l-α-p-hydroxyphenylethylmethylamine which crystallises from/

from the same solvent and melts at the same temperature. The rotations of these bases were not measured, but the hydrochlorides which crystallise from alcohol and melt at 180° were examined with the following results. In each case 0.2000 gm. was dissolved in 2 c.c. of water and the rotation determined in a decimeter tube. The hydrochloride derived from the tartrate, m.p. 162° gave $\alpha_D = 2.23°$ and that derived from the tartrate, m.p. 133° gave $\alpha_D = -2.20°$.

In conclusion the author wishes to record his appreciation for the helpful guidance and encouragement shown him by Dr E. Stedman throughout the course of this work.